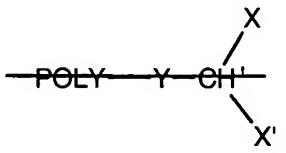
In the Specification:

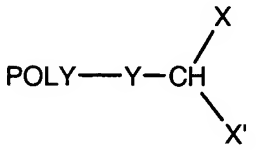
Please amend the specification as indicated below. Within the cited text in which an amendment is desired, a ~~strikethrough~~ or double brackets (e.g., [[error]]) is provided for deleted matter. Underlining is provided for added matter except when underlining has been preserved from the original text (e.g., when referring to protons corresponding to NMR signals).

Please amend the paragraph on page 1, beginning at line 3, as follows:

This application is a continuation of U.S. Application Serial No. 09/992,102, filed November 5, 2001, which is a divisional of U.S. Application Serial No. 09/265,989, now U.S. Patent ~~No. _____, filed on Mar. 11, 1999~~ No. 6,362,254, filed on March 11, 1999, which is related to Provisional Application Serial No. 60,077,700, filed March 12, 1998, and claims the benefit of its filing date under 35 U.S.C. §119(e). ~~Both~~ All applications are incorporated by reference herein in their entirety.

Please amend the structure appearing on page 5, line 7, as follows:





Please amend the paragraph on page 6, beginning at line 12, as follows:

Many central branch core molecules for preparing branched or dendritic PEGs are known and can all be used for R. Typically, R can be a moiety derived from lysine, glycerol, pentaerythritol, or sorbitol. Suitable polymer backbones include, but are not limited to, linear and branched poly(ethylene glycol), linear and branched poly(alkylene oxide), linear and branched poly(vinyl pyrrolidone), linear and

branched poly(vinyl alcohol), linear and branched polyoxazoline, linear and branched poly(acryloylmorpholine), and derivatives thereof. Preferably, [[is]] poly(ethylene glycol) or a derivative thereof is used as the polymer backbone.

Please amend the paragraph bridging pages 8 and 9 as follows:

Poly(ethylene glycol) or PEG is useful in biological applications because it has properties that are highly desirable and is generally approved for biological or biotechnical applications. PEG typically is clear, colorless, odorless, soluble in water, stable to heat, inert to many chemical agents, does not hydrolyze or deteriorate, and is generally nontoxic. Poly(ethylene glycol) is considered to be biocompatible, which is to say that PEG is capable of coexistence with living tissues or organisms without causing harm. More specifically, PEG is non-immunogenic, which is to say that PEG does not tend to produce an immune response in the body. When attached to a molecule having some desirable function in the body, such as a biologically active agent, to form a conjugate, the PEG tends to mask the agent and can reduce or eliminate any immune response so that an organism can tolerate the presence of the agent. Accordingly, the conjugate is substantially non-toxic. PEG conjugates tend not to produce a substantial immune response or cause clotting or other undesirable effects. PEG having the formula ~~$-CH_2CH_2-(CH_2CH_2O)_n-CH_2CH_2-$~~ $-CH_2CH_2O-(CH_2CH_2O)_n-CH_2CH_2-$, where n is from about 8 to about 4000, is one useful polymer in the practice of the invention. Preferably PEG having a molecular weight of from about 200 to about 100,000 Da is used as a polymer backbone.

Please amend the paragraph on page 10, beginning at line 6, as follows:

Many ~~other~~ water soluble substantially non-immunogenic polymers other than PEG are also suitable for the present invention. These other polymers can be either in linear form or branched form, and include, but are not limited to, other poly(alkylene oxides) such as poly(propylene glycol) ("PPG"), copolymers of ethylene glycol and propylene glycol and the like; poly(vinyl alcohol) ("PVA") and the like. The polymers can be homopolymers or random or block copolymers and terpolymers

based on the monomers of the above polymers, straight chain or branched.

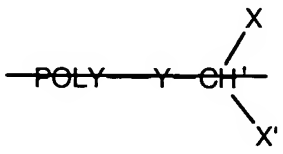
Please amend the paragraph on page 10, beginning at line 22, as follows:

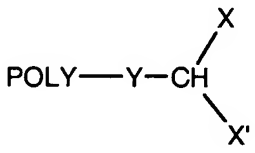
Those of ordinary skill in the art will recognize that the foregoing list for substantially water soluble non-immunogenic polymer ~~backbone~~ backbones is by no means exhaustive and is merely illustrative, and that all polymeric materials having the qualities described above are contemplated.

Please amend the paragraph on page 11, beginning at line 15, as follows:

At least one of the two free reactive groups may comprise two portions: a reactive moiety at the free end and a tethering group linking the reactive moiety to the branching moiety. The reactive moiety is a moiety capable of reacting with a moiety in another molecule, e.g., a biologically active agent such as ~~proteins~~ a protein, ~~peptides~~ a peptide, etc. Examples of suitable reactive moieties include, but are not limited to, active esters, active carbonates, aldehydes, isocyanates, isothiocyanates, epoxides, alcohols, maleimides, vinylsulfones, hydrazides, dithiopyridines, N-succinimidyl, and iodoacetamides. The selection of a free reactive moiety is determined by the moiety in another molecule to which the free reactive moiety is to react. For example, when the moiety in another molecule is a thiol moiety, then a vinyl sulfone moiety is preferred for the free reactive moiety of the activated polymer. On the other hand, an N-succinimidyl moiety is preferred to react to an amino moiety in a biologically active agent.

Please amend the structure appearing on page 12, line 6, as follows:





Please amend the paragraph on page 13, beginning at line 28, as follows:

Typically, in the first step, there is a first intermediate polymer provided having a polymer backbone and a reactive end group covalently linked to [[of]] the polymer backbone.

Please amend the paragraph on page 15, beginning at line 15, as follows:

Other moieties in biologically active agents useful for reacting with the free reactive moieties of the bivalent terminus of an activated polymer of this invention include, e.g., amino groups, carboxylic acid groups, etc. It will be apparent ~~for~~ to the skilled artisan once apprised of the present invention to select appropriate free reactive moieties in an activated polymer for reaction with a given moiety in a biologically active agent. For example, if conjugation is through reaction with an amino group in a biologically active agent, moieties such as -CO_2-NS or aldehyde ~~is~~ are preferably used as a free reactive moiety in the activated polymer for conjugation.

Please amend the Example on page 16, line 8, as follows:

Example 4. Synthesis of ~~mPEG$_{5k}$-O-CH$_2$CH$_2$CH(CO$_2$H)$_2$~~ mPEG$_{5K}$-O-$CH_2CH_2CH(CO_2H)_2$

Please amend the paragraph bridging pages 16 and 17 as follows:

A solution of mPEG$_{20K}$-$OCH_2CH_2CO_2NS$ (mSPA 20K, 20 g, 0.001 moles)[[)]], $H_2NCH(CH_2\text{-}OH)_2$ (serinol, [[,]] 0.14 g, 0.00154 moles), and triethylamine (0.3 ml) in acetonitrile (100 ml) was stirred under nitrogen overnight and the solvent removed by distillation. The product was chromatographed on DEAE sepharose eluted with water and the eluate was saturated with NaCl and extracted with chloroform. The resulting chloroform phase was dried over magnesium sulfate, filtered, and the filtrate evaporated to dryness under vacuum to yield 20 g of product as a white solid showing a single peak with gel permeation chromatography (Ultrahydrogel 250, pH 7.2 buffer).

Please amend the paragraph on page 17, beginning at line 8, as follows:

A solution of the product from (1) (20 g, 0.002 moles) and butylated hydroxytoluene (BHT) (0.02g) in 220 ml of chloroform was subjected to distillation until about 150 ml of solvent had distilled. Succinic anhydride (2.0 g, 0.02 moles), pyridine (1.62 ml, 0.02 moles), and 40 ml of toluene were added and the resulting mixture heated at ~~84 □C~~ 84 °C for 20 h under nitrogen. The product was precipitated with 850 ml of ether and collected by filtration. After drying, the product was dissolved in 200 ml of water, 20 g of NaCl added, and the pH adjusted to 3 with aqueous phosphoric acid. The product was extracted with chloroform (200+150+100 ml) and the combined extracts dried over magnesium sulfate. Evaporation of the dried solution yielded the product as a white solid (16 g). The molecular weight was determined to be 20,940 Da by potentiometric titration.

Please amend the paragraph on page 18, beginning at line 22, as follows:

A solution of 18 g (0,0641 moles) of 1,3-dibenzyloxy-2-propanol in 80 ml of toluene was distilled until 15 ml of toluene was removed. The azeotropically dried solution was then added to a suspension of 2.56 g (0.064 moles) of NaH in 80 ml of toluene and the resulting mixture stirred while heating to ~~37-40 □C~~ 37-40 °C before filtering. The filtrate was then added to a solution of azeotropically-dried $mPEG_{20K}$ mesylate in about 350 ml of toluene and the resulting mixture was heated for 20 h at ~~125 □C~~ 125 °C under N_2. The product was precipitated with cold ether, wash on the filter with hexane, and dried under vacuum to yield 70.4 g of white solid shown to be pure by proton nmr.

Please amend the paragraph on page 19, beginning at line 20, as follows:

A solution of the product of (3), (7.0 g, 0.00035 moles), mercaptoethanol (0.56, 0.0080 moles) [[ml]], NaOH (0.22 g), in toluene ~~(30 ml~~ (30 ml) and ethanol (60 ml) was heated at ~~60 □C~~ 60 °C for 2 h under N_2. The pH was adjusted to 7 and the product extracted with methylene chloride (3x100 ml). After drying the extract over ~~MgSO4~~ $MgSO_4$, the solvent was removed and the product precipitated with 250 ml of ethyl ether. The product was collected by filtration and dried under vacuum to get 6.6 g of white solid which was shown by nmr to be 97.3% substituted.

Please amend the paragraph bridging pages 19 and 20 as follows:

A solution containing the product from (4), 6.5 g (0.00065 moles), and tungstic acid (0.16 g) in water (14 ml) was prepared and the pH adjusted to 6.6. Hydrogen peroxide (30%, 0.65 ml) was added and the mixture stirred at room temperature overnight. The pH was adjusted to 7.5 and the mixture stirred 1 h before extracting with CH_2Cl_2 (3x30 ml). The mixture was dried over ~~MgSO4~~ $MgSO_4$, filtered, and the filtrate concentrated to 25 ml. The product was precipitated with 200 ml of ether and collected by filtration to obtain 5.3 g of product after vacuum drying. The product was shown by nmr to have 86% substitution.

Please amend the paragraph on page 20, beginning at line 9, as follows:

A solution of the product from (5), (5.2 g, 0.00052 moles), Et_3N (0.63 ml, 0.00452 moles), BHT (0.005 g), and MsCl (0.15 ml, 0.001938 moles) in CH_2Cl_2 (25 ml) was stirred at room temperature for 42 h at room temperature. Ethanol (1 ml) was added and the mixture was stirred 15 minutes. Methylene chloride (50 ml) was added and the resulting solution was washed with aqueous 1M HCl followed by 5% aqueous Na_2HPO_4. After drying over ~~MgSO4~~ $MgSO_4$, the solution was concentrated to 30 ml and the product precipitated with 300 ml of ether. The product was collected by filtration and dried under vacuum to yield the product (4.6 g) as a white solid. The degree of substitution was 92.5% by nmr. The ^1H nmr spectrum (dmso-d6) displayed absorptions at 3.51 ppm (PEG backbone CH_2), 3.23 ppm[[,]] (CH_3O), 6.2 and 7.0ppm [[,]] (m, vinyl H). Note in this example that Y=O, W=CH_2, and Z=$SO_2CH{=}CH_2$.

Please amend the paragraph on page 21, beginning at line 4, as follows:

To a solution of β-glutamic acid (0.10 g, 0.00068 moles), boric acid (0.1 g) in 10 ml of water at pH 8 was added $mPEG_{5K}BTC$ over 15 m while maintaining the pH at 8.15-8.25 by addition of NaOH solution. NaCl (6 g) was added and the pH of the solution was adjusted to 2 with 10% H_3PO_4. The product was extracted into CH_2Cl_2 (100+80+50 ml) and the combined extracts were dried over $MgSO_4$. The mixture was filtered and the filtrate evaporated under vacuum to yield

7.8 g of product. The mixture was determined to be 75.5% of the mPEG glutamic acid derivative and 24.5% mPEG. This mixture was purified by chromatography on DEAE sepharose by first eluting with water and then eluting the desired product with 0.5 M NaCl. Extraction of the product from the NaCl solution (pH 2) with methylene chloride followed by drying the extract over ~~MgSO4~~ $MgSO_4$ and evaporation of the solvent yielded 6.1 g of material shown to be 100% pure by GPC.

Please amend the paragraph on page 21, beginning at line 17, as follows:

A solution of $mPEG_{5K}O_2CNHCH(CH_2CO_2H)_2$ (6.0 g, 0.00116 moles), NHS (0.385 g, 0.001627 moles), DCC (0.676 g, 0.00162 moles) in methylene chloride (50 ml) was stirred overnight at room temperature under nitrogen. The resulting suspension was filtered and the filtrate was added to 500 ml of cold ethyl ether. The precipitate was collected by filtration and dried under vacuum to obtain 5.5 g of product which was shown by nmr to have 100% substitution. The ^1H nmr spectrum (dmso-d6) displayed absorptions at 3.51 ppm (PEG backbone CH_2), 3.23 ppm[[,]] (CH_3O), 4.29 ppm (-NHCH-), 4.05 ppm (-CH_2-O-CONH-), 3.24 ppm ($CH_2CO[[2]]_2NS$), 2.81 (NS CH_2).

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